Time Trends in Survival Following First Hemorrhagic or Ischemic Stroke Between 1991 and 2015 in the Rotterdam Study

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Background and Purpose—The introduction of stroke units and the implementation of evidence-based interventions have been a breakthrough in the management of patients with stroke over the past decade. Survival following stroke is an important indicator in monitoring stroke burden. Recent data on survival by stroke subtype in the general population is scarce. We assessed (1) recent temporal time trends in survival; (2) age-standardized death rates; (3) survival probabilities at 6 months, 1, 2, and 3 years following first hemorrhagic or ischemic stroke.

Methods—Within the population-based Rotterdam Study between 1991 and 2015, we assessed time trends in survival among 162 with first-ever hemorrhagic and 988 patients with first-ever ischemic stroke across 3 time periods (1991–1998; 1999–2007; 2008–2015) using time-varying Cox regression model and calculated age-standardized death rates according to the European 2010 census population.

Results—In the hemorrhagic stroke group, a total of 144 deaths occurred during 386 person-years. Following a hemorrhagic stroke, we observed similar mortality rates over the years with 30 per 100 person-years in 2015 compared with 25/100 person-years in 1991. Similarly, compared with the earliest study period (1991–1998), mortality rates remained unchanged in the latest study period (2008–2015; hazard ratio, 0.97 [95% CI, 0.61–1.57]; P=0.93). In the ischemic stroke group, a total of 711 deaths occurred during 4897 person-years. We observed a decline in mortality rates in 2015 (11 per 100 person-years) compared with 1991 (29/100 person-years). This translated to favorable trends in the latest study period 2008 to 2015 (hazard ratio, 0.71 [95% CI, 0.56–0.90]; P<0.01).

Conclusions—Survival following ischemic stroke has improved over the past decade, while no change was observed in survival following hemorrhagic stroke. **(*Stroke*. 2020;51:824-829. DOI: 10.1161/STROKEAHA.119.027198.)**

Key Words: hemorrhagic ■ ischemic ■ population ■ prognosis ■ stroke ■ survival ■ trends

Over the past decade, major advances in clinical neurology (eg, stroke units and neuroimaging techniques) have distinctively improved timely diagnosis and management of stroke and its major subtypes.[1] However, it remains unclear whether this progress translates into improved survival for both hemorrhagic and ischemic stroke in the general population.

Survival following stroke is an important indicator in monitoring stroke burden.[2] Several studies have observed decline in mortality after any stroke.[3–6] However, up-to-date country-specific survival data by stroke-subtype are scarce. Although there is agreement on the increased risk of mortality following a stroke, recent data on time trends in survival in the general population, especially for hemorrhagic stroke, are limited.

Prospective studies provide an opportunity for precise monitoring of the burden related to stroke-subtypes in unselected samples of patients. This is in contrast to hospital-based data where the following inherent limitations exist: (1) selection bias related to indication for admission according to stroke severity and prognosis; (2) potential differential access to specialized stroke units; and (3) variation between centers in quality of in-patients care and services provided. These factors influence outcomes of patients with stroke and therefore hospitalizations data may not reflect the real burden of the disease in the population.

Regular monitoring of trends in survival by stroke-subtype is necessary to monitor the disease burden at a population level.[7] In this report, we characterized temporal trends in survival following hemorrhagic or ischemic stroke using a large population-based sample of middle-aged and elderly people over 20 years of follow-up.

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Methods

Study Settings

The Rotterdam Study

This study included participants from the Rotterdam Study, a prospective community-based cohort study.[8] In 1990, residents aged 55 years and older residing in Ommoord, a district of Rotterdam, the Netherlands, were invited to participate in the study. Of 10 215 invited inhabitants, 7983 agreed to participate in the baseline examinations. In 2000, 3011 participants (of 4472 invitees) who had reached 55 years of age or moved into the study district since the start of the study were added to the cohort. In 2006, a further extension of the cohort was started in which 3932 participants, of 6057 invited, aged at least 45 years living in Ommoord were included. Follow-up examinations take place every 3 to 4 years. For the purpose of the present study, we excluded patients with unspecified stroke diagnosis.

Informed Consent and Ethics Approval

The Rotterdam Study has been approved by the medical ethics committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). When visiting the study center, participants provided written informed consent to participate in the study and to have their information obtained from treating physicians. Requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to Department of Epidemiology, Erasmus MC University Medical Center at f.vanrooij@erasmusmc.nl.

Stroke Assessment and Follow-Up

Stroke was defined according to the World Health Organization criteria as a syndrome of rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin.[8–10] History of stroke at baseline was assessed during baseline interview and verified by reviewing medical records. After enrollment, participants were continuously monitored for incident stroke through automated linkage of the study database with files from general practitioners. Nursing home physicians' and general practitioner files of participants who moved out of the district were checked on a regular basis as well. Additional information was obtained from hospital records. Potential strokes were reviewed by research physicians and verified by an experienced neurologist. Stroke subtype (hemorrhagic or ischemic), location, cause, and other stroke specific characteristics were based on neuroimaging reports and hospital discharge letters. If these were absent, then the stroke subtype was classified as unspecified. This classification corresponded with *International Classification of Diseases Tenth Version* codes I61, I63, and I64. Participants could contribute person-years to the follow-up that is, from date of first stroke diagnosis until death, loss to follow-up, or end of study period (January 1, 2016), whichever came first. Follow-up was virtually complete (95.8%).

Mortality

Information on vital status of participants was obtained on a weekly basis via municipal population registries and through general practitioners' and hospitals' databases. Events were coded according to the *International Classification of Diseases Tenth Version* by 2 independent research physicians. All-cause mortality was defined as participants who died from any cause during the total follow-up period, which was completed until January 1, 2016.

Statistical Analysis

Baseline characteristics were summarized as median (interquartile range) for continuous variables and frequencies and percentages for categorical variables. Two types of analysis were undertaken. First, time-varying Cox proportional hazards regression analysis was used to assess mortality rates following first-ever hemorrhagic or ischemic stroke across the following 3 main study periods: 1991 to 1998, 1999 to 2007, and 2008 to 2015. Models were adjusted for sex and age at stroke diagnosis. Models fit was assessed based on Akaike Information Criterion. Second, age-standardized mortality rates per 100 person-years stratified by stroke subtype were calculated according to the age distribution in the standard European population in 2010 using 5-year age groups.[11] Individuals who died on the same day of their stroke diagnosis contributed 1 day of follow-up in the analysis. We further assessed survival probabilities at 6 months, 1, 2, and 3 years in both groups and in a control group of stroke-free cases matched on age and sex to the overall stroke group. Analyses were performed using the Stata v15.0 (StataCorp, College Station, TX).

Results

Population Characteristics

Hemorrhagic Stroke

Over the study period between 1991 and 2015, among 162 hemorrhagic strokes, a total of 144 deaths occurred during 386 person-years. In the hemorrhagic group, 59 % were women, median age at time of stroke diagnosis was 79 (72–85) years, and median age at death was 82 (77–87) years (Table 1).

Among the cases for which a cause was specified (n=62 [38%]), anticoagulant-related hemorrhagic stroke and amyloid angiopathy represented the majority of cases (n=36), followed by hypertension (n=11). The majority of cases with an identified location were lobar (n=49) or deep (n=25; Figure 1).

Ischemic Stroke

Over the study period between 1991 and 2015, among 988 ischemic strokes, a total of 711 deaths occurred during 4897 person-years. In the ischemic stroke group, 56% were women, median age at time of stroke diagnosis was 78 (72–84) years, and median age at death was 84 (79–89) years (Table 1).

Time Trends in Survival Following Hemorrhagic Stroke

Absolute death counts and age-standardized mortality rates remained unchanged over the study period following hemorrhagic stroke (Figure 1). In adjusted Cox proportional hazards models, compared with the earliest study period (1991–1998),

Table 1. Descriptive Characteristics of the Population

	Hemorrhagic Stroke	Ischemic Stroke
N	162	988
Age at stroke date, y	79.6 (12.8)	78.2 (11.7)
Women	96 (59.3)	556 (56.3)
BMI, kg/m^2	26.1 (4.9)	26.9 (4.4)
Cholesterol, mmol/L	5.8 (1.2)	5.9 (1.6)
Diabetes mellitus type 2	30 (28.6)	192 (29.1)
Hypertension	123 (82.6)	767 (83.9)
Smoking		
Current	32 (21.2)	232 (25.0)
Former	75 (49.7)	387 (41.7)
Never	44 (29.1)	308 (33.2)

Categorical: number (percentage). Continuous: median (interquartile range); for all characteristics (except age at stroke diagnosis and sex), the values were derived from the visit to the research center that was before the date of stroke; missing covariate data in the hemorrhagic and ischemic stroke groups were as follows: BMI (8%, 10%); cholesterol (10%, 9%); DM (35%, 33%); hypertension (8%, 7%); smoking (7%, 6%); reasons for missing covariate data: (1) participants did not visit the research center before their first stroke date (2) or data were missing at baseline and subsequent visits. BMI indicates body mass index; and DM, diabetes mellitus.

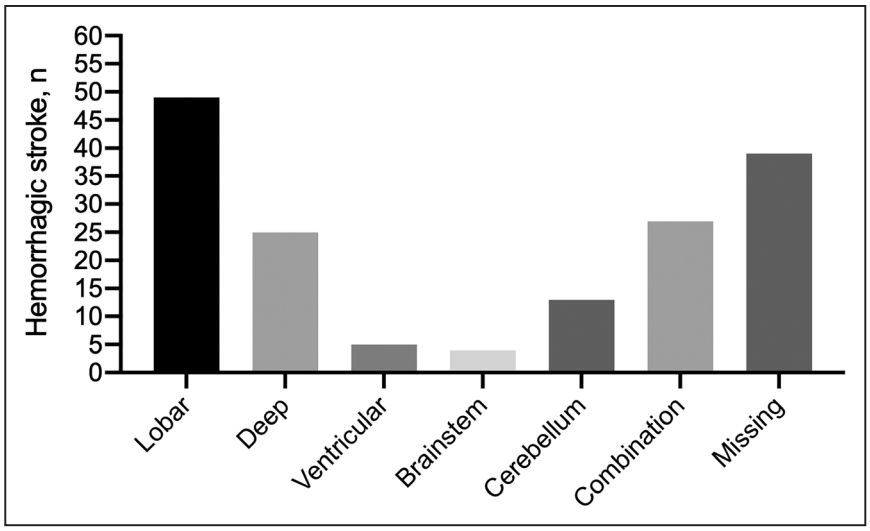


Figure 1. Location of hemorrhagic stroke.

mortality rates following hemorrhagic stroke remained unchanged in 1999 to 2007 (adjusted hazard ratio, 0.88 [95% CI, 0.56–1.38]) and 2008 to 2015 (adjusted hazard ratio, 0.98 [95% CI, 0.61–1.57]; Table 2).

Time Trends in Survival Following Ischemic Stroke

The absolute death counts continued to increase with the aging of our population. A steady decline was observed overtime in the age-standardized mortality rates over the study period following ischemic stroke (Figure 2). Mortality rates following ischemic stroke declined in the later study periods in 1999 to 2007 (adjusted hazard ratio, 0.85 [95% CI, 0.67–1.06]) and 2008 to 2015 (adjusted hazard ratio, 0.71 [95% CI, 0.56–0.90]) compared with the earliest study period (1991–1998; Table 2).

Survival Probabilities Following Hemorrhagic or Ischemic Stroke

In the hemorrhagic stroke group, survival probabilities were as follows: 6 months (36% [95% CI, 28–43]), 1 year (34% [95% CI, 27–41]), 2 years (31% [95% CI, 24–38]), and 3 years (27% [95% CI, 20–33]).

In the ischemic stroke, estimates were as follows: at 6 months (81% [95% CI, 78–83]), 1 year (76% [95% CI, 73–78]), 2 years (68% [95% CI, 65–71]), and 3 years (61% [95% CI, 58–64]).

Among the age- and sex-matched stroke-free controls, survival probabilities were: 96% (95% CI, 94–97) at 6 months; 93% (95% CI, 92–95) at 1 year, 87% (95% CI, 85–89) at 2 years, and 82% (95% CI, 80–84) at 3 years (Figure 3). Survival probabilities in the control group remained high over the 25 years of follow-up (Figure I in the online-only Data Supplement).

Discussion

We observed favorable trends in survival following ischemic stroke. In contrast, mortality rates following hemorrhagic stroke remained high.

There are several factors that could have contributed to the observed favorable trends in survival following ischemic stroke in our study and the observed decline in mortality after any stroke in other settings.[3,5,6,12] First, the introduction of stroke units providing timely acute medical management and dedicated rehabilitation.[13,14] Furthermore, among eligible patients, thrombolytic therapy within the first 6 hours has been associated with less death and dependence despite a relative increase in symptomatic intracranial hemorrhage.[15] In addition, reduction of in-hospital mortality has been reported among patients with shorter time to endovascular-reperfusion therapy in routine clinical practice.[16] Second, the availability of high-quality evidence and guidelines on best practices in the acute phase, particularly on postacute stroke management in recent years.[17] Third, the improved control of risk factors and timely counseling after stroke.[18]

Recent reports further emphasize the role played by stroke units and advances in stroke care in reducing stroke-related mortality and case fatality.[13,14,19] In the Netherlands, major advances in stroke care were introduced since mid-nineties and continued to be widely implemented after 2000 including stroke units, thrombolytic therapy, and stroke prevention guidelines.[19–21]

Despite this decline in mortality rates, the absolute numbers of deaths after stroke and the numbers of patients in need of care and intensive treatment is unlikely to diminish in the near future, owing to the rise in aging populations globally.[12] In fact, the favorable trends observed after ischemic stroke will likely gradually translate to a greater accumulated burden of disability and stroke-related dependency.[3,22–24]

A majority of patients with stroke suffer from one or more disability after recovery including hemiparesis (≈50%), cognitive deficits (46%), aphasia (19%), depression (35%), and limitations with walking unassisted (30%).[25] Several reports showed an increase in long-term institutionalization, in-patient rehabilitation services, support services after discharge, and informal care giving among stroke survivors.[3,23–25]

Stroke is ranked as one of the most expensive diseases in the Netherlands.[26] The burden of stroke-related disability and the associated costs are expected to continue to increase in aging populations. Beyond professional care giving and institutionalization costs, data from the American Heart Association showed that costs of informal care giving alone

Table 2. Cox Regression Model of Time to Death Following Hemorrhagic or Ischemic Stroke

	Hemorrhagic Strokes, N=162				Ischemic Strokes, N=988			
	Deaths, n	Person-Years*	aHR† (95% CI)	*P* Value	Deaths, n	Person-Years	aHR† (95% CI)	*P* Value
Study period								
1991–1998	30	38	…	…	110	635	…	…
1999–2007	60	163	0.88 (0.56–1.38)	0.60	294	2031	0.85 (0.67–1.06)	0.16
2008–2015	54	184	0.98 (0.61–1.57)	0.93	307	2230	0.71 (0.56–0.90)	<0.01

*aHR indicates adjusted hazard ratio.

†Person-years represent the unit for the population in each calendar period in a time-varying fashion.

‡Models are adjusted for age at stroke diagnosis and sex.

constitute more than half of the total costs of cardiovascular disease combined, with an estimated 31$ billion in 2015 and 66$ billion in 2035.[27] Hence, reducing stroke-related disability is becoming an increasingly fundamental target to significantly reduce stroke burden in high-risk populations.[12]

In contrast to ischemic stroke, a fewer successful therapeutic options exist for hemorrhagic stroke.[28] Poor outcomes following hemorrhagic stroke are linked to the complications that arise shortly following onset. Hematoma expansion and early deterioration are common within the first few hours. Further, hematoma volume, deep location, and extension of bleeding into the ventricular system have been linked to poor neurological outcomes.[28,29]

To date, no successful phase 3 clinical trials have been documented for therapeutic options among hemorrhagic stroke survivors. This research gap highlights the importance of targeting complications during the acute phase of the disease, given that patients are highly likely to be unstable shortly after onset. Current evidence supports admitting hemorrhagic stroke survivors to a dedicated stroke unit rather than general intensive-care unit.[30] This is particularly essential given the lack of therapeutic options; hence, prevention or early detection of complications could be the most effective approach to improve outcomes after hemorrhagic stroke.[31]

Recent estimates from the STICH trial (Early Surgery Versus Initial Conservative Treatment in Patients With Spontaneous Supratentorial Lobar Intracerebral Haematomas) showed improved 6-month mortality rates in patients who received early surgical hematoma evacuation within 12 hours of randomization plus medical treatment (18%) compared with initial medical treatment alone (24%).[32] Data of the MISTIE trial (Safety and Efficacy of Minimally Invasive Surgery Plus Alteplase in Intracerebral Haemorrhage Evacuation) showed no difference at 6 months in the proportion of patients with modified Rankin Scale score of 6 between minimally invasive surgery plus alteplase compared with standard medical care.[33] Although these interventions show promise in selected samples of patients in the setting of clinical trials, these advances are not yet reflected in the setting of the general population. In our study, 6-month mortality rate in the hemorrhagic stroke group was 64%, and comparable estimates were reported from the Swedish stroke register with ≈60% mortality rate at 12

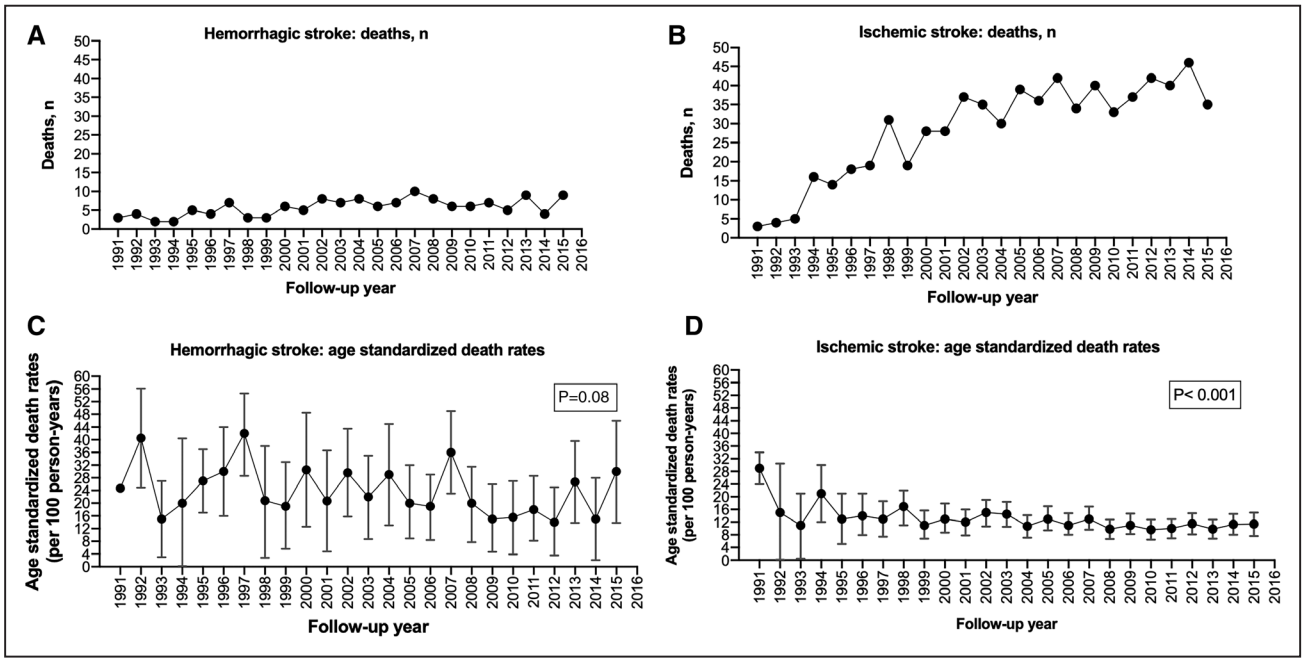
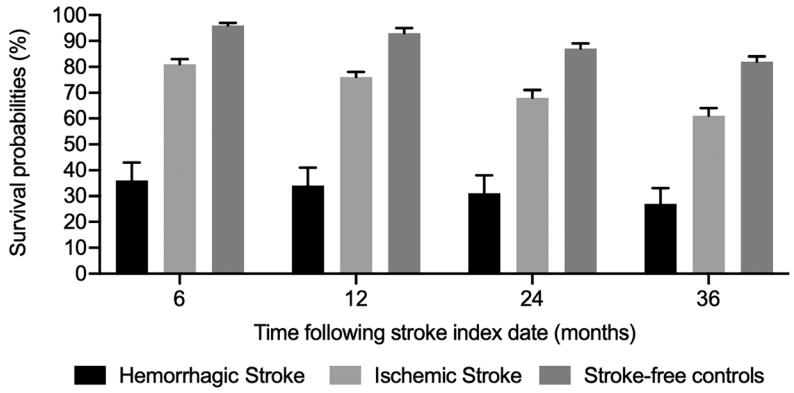


Figure 2. Absolute death counts and age standardized death rates per 100 person-years following hemorrhagic or ischemic stroke. *P* value test for trend across calendar year.



Time	Survival probability (95% CI)		
	Hemorrhagic stroke	Ischemic stroke	Control group*
6 months	36% (28% - 43%)	81% (78% - 83%)	96% (94% - 97%)
1 year	34% (27% - 41%)	76% (73% - 78%)	93% (92% - 95%)
2 years	31% (24% - 38%)	68% (65% - 71%)	87% (85% - 89%)
3 years	27% (20% - 33%)	61% (58% - 64%)	82% (80% - 84%)

**Controls and stroke cases were matched on year of birth and sex; each control was used only once.*

Figure 3. Survival probabilities at 6, 12, 24, and 36 mo following hemorrhagic or ischemic stroke.

months among those with functional dependence and 42% among all intracerebral hemorrhage cases.[22]

The decline in mortality after ischemic stroke in our study aligns with the decline of coronary heart disease mortality observed in the Netherlands and in other countries.[34,35] Cardiovascular disease is a leading cause of death in the Rotterdam study population and nationwide in the Netherlands.[36–40] In 2017, ischemic heart disease and stroke ranked as first and third causes of years of life lost worldwide.[41,42] Collectively, these observations highlight the need for continuous efforts targeted toward prevention of stroke and ischemic heart disease, particularly in the setting of elderly populations.

Our study has several limitations. Our sample included a proportion of unspecified strokes and thus were not included in the analysis. This could have resulted in underestimation of mortality rates; however, the consistency in trends among the classified cases is reassuring and the exclusion of those cases is not uncommon in stroke-subtype investigations.[43] Further, the limited power among cases with identified location or cause in the hemorrhagic stroke group hindered conducting a stratified or subgroup analysis. However, among the classified cases, the majority were of lobar location or related to anticoagulants and amyloid angiopathy. Similar observations have been reported from the United Kingdom and the United States.[44,45] Last, our sample is restricted to stroke survivors among the elderly, thus cannot be extrapolated to younger stroke survivors.

Alongside the long follow-up duration and state-of-the-art clinical examinations, a key strength of our study includes the unselected sample of participants who were followed up prospectively, thus avoiding common biases related to institution or patient selection. These factors all together provide a close reflection of the current disease burden in the population.

Conclusions

In this report, we observed marked improvement in survival following ischemic stroke since early 2000s, in contrast no improvement in survival following hemorrhagic stroke was observed.

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Disclosures

None.

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